Evaluation of Cardiac Function in Uncomplicated COVID-19 Survivors by 2-Dimensional Speckle Tracking Imaging

ABSTRACT

Background: COVID-19 is a multi-systemic infectious disease. Nearly 20%-30% of hospitalized patients have evidence of acute myocardial involvement, portending a poorer prognosis. However, information about the long-term effects of the disease on cardiac functions is sparse. As a result, there is a growing concern about the cardiac sequelae of COVID-19 among survivors. This study aimed to investigate the effects of prior mild-moderate COVID-19 infection on cardiac functions, using speckle tracking echocardiography.

Methods: Patients who have been diagnosed with COVID-19 within the previous 6 months and age-, sex-, and risk factor-matched healthy adults were included. All patients underwent a comprehensive echocardiographic examination. Both conventional and 2-dimensional speckle tracking echocardiographic measurements were performed. Serum cardiac biomarkers were also obtained on the day of the echocardiographic study.

Results: Compared with healthy controls, COVID-19 survivors had similar left and right ventricular longitudinal strain values at 6 months. Also, left and right atrial peak systolic strain values did not differ between the groups.

Conclusion: Our study is valuable in putting forth the unaffected ventricular and atrial functions on long term in uncomplicated COVID-19 cases and may decrease the survivors' anxiety and the number of unnecessary applications to cardiology clinics.

Keywords: COVID-19, echocardiography, 2-dimensional speckle tracking imaging

ORIGINAL INVESTIGATION

INTRODUCTION

Since the announcement of the first case in Wuhan, China, in December 2019, the world has been facing a global healthcare crisis called the "COVID-19 pandemic." COVID-19 is an infectious disease, with clinical manifestations ranging from asymptomatic infection to acute respiratory distress syndrome (ARDS) and death.[1] Following respiratory involvement, the cardiovascular system is the second most affected organ in the human body. The cardiac manifestations of COVID-19 infection include acute myocardial injury, acute myocarditis, myocardial infarction (type 1 and 2), arrhythmias, heart failure, stress cardiomyopathy, and thromboembolic diseases.[2] Acute myocardial injury, characterized by the presence of at least 1 cardiac troponin value above the 99th percentile upper reference limit, is the most common cardiac complication of acute COVID-19 infection. A recent meta-analysis reported the incidence of acute myocardial injury as 22.33% among infected patients.[3] The underlying causes of acute myocardial injury during COVID-19 may include myocarditis, stress cardiomyopathy, arrhythmias, and myocardial infarction, though most of the time, the definitive cause could not be identified.[2]

Approximately 20%-30% of hospitalized patients have evidence of some degree of acute myocardial injury, strongly correlated with in-hospital mortality.[4] In addition, previous studies have revealed clinical or sub-clinical biventricular systolic dysfunction associated with a poorer prognosis.[5-7] Today, it is still not clear

Müge Akbulut [ID]
Seda Tan [ID]
Demet Menekşe Gerede Uludağ [ID]
Volkan Kozluca [ID]
İrem Dinçer [ID]

Department of Cardiology, Faculty of Medicine, Ankara University, Ankara, Turkey

Corresponding author:
Demet Menekşe Gerede Uludağ
✉ drmeneksegerede@yahoo.com

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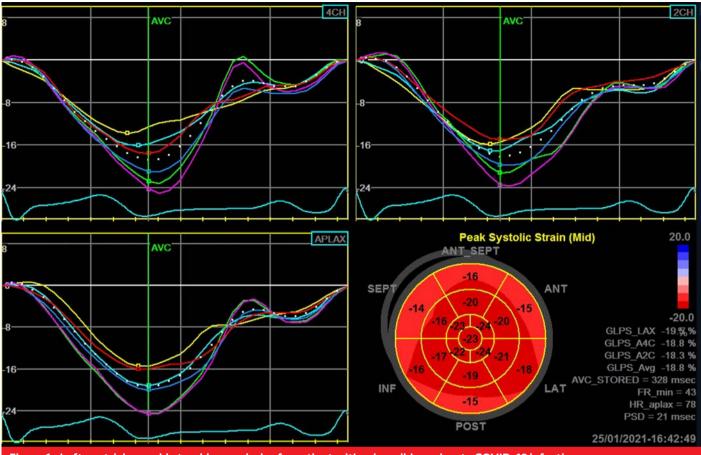
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Figure 1. Left ventricle speckle tracking analysis of a patient with prior mild-moderate COVID-19 infection.

whether the myocardial involvement results from direct viral invasion or the systemic inflammatory response.

On the other hand, not much is known about the long-term cardiac effects of COVID-19 infection. Some small-scale studies conducted in patients who recently recovered from uneventful COVID-19 set forth subtle findings and ongoing myocardial inflammation of unknown clinical significance on cardiac magnetic resonance imaging (MRI).[8,9] Contrarily, a very recent study from Joy et al[10] revealed no cardiac involvement in mild COVID-19 survivors 6 months after the initial infection. Recently, there has been an increasing concern about long-term cardiac sequelae of COVID-19 among survivors and a growing number of applications to outpatient cardiology clinics with this concern.

HIGHLIGHTS

- Uncomplicated COVID-19 infection had no measurable effect on both ventricular and atrial functions on long term.
- Troponin-I and NT-proBNP, biomarkers of myocardial injury, levels were within the normal limits, illustrating the absence of ongoing myocardial injury on long term.

Two-dimensional speckle tracking echocardiography (2D-STE) has been widely used to detect sub-clinical myocardial impairment earlier, with the advantages of being angle-independent and less influenced by loading conditions. The global longitudinal strain (GLS) values of both left and right ventricle (RV) acquired with 2D-STE dimensional speckle tracking echocardiography provide crucial prognostic information in various cardiac disease states.[11,12] Furthermore, atria's longitudinal strain has recently gained popularity in predicting ventricular filling pressures and diastolic function.[13]

This study aimed to investigate the cardiac functions in mild-moderate COVID-19 survivors without any documented acute cardiac events during the initial infection, by using speckle tracking echocardiography.

METHODS

Study Population
In this prospective study, a total number of 75 patients who applied to our outpatient cardiology clinic for varying complaints between September 2020 and December 2020 and have been diagnosed with COVID-19 infection within the previous 6 months of the application were screened. All participants were considered eligible after the end of the isolation period. Twelve patients were excluded from preexisting atherosclerotic heart disease, and 5 were excluded

due to poor echocardiographic views. Of the screened patients, we included a total of 58 patients. The inclusion criteria for the patients were as follows:

1. age between 18 and 70;
2. having been diagnosed with COVID-19 infection based on real-time reverse-transcription polymerase chain reaction (RT-PCR) results within the previous 6 months and no acute cardiac events were noted during the infection;
3. having no known cardiac disease (coronary artery disease, valvular heart disease, arrhythmias).

Patients younger than 18 years or older than 70 years, patients with a previous history of valvular heart disease, coronary artery disease, arrhythmia, chronic pulmonary diseases, and renal failure were excluded from the study. Mild COVID-19 infection was defined as individuals having various symptoms but not dyspnea or abnormal chest CT scan. Moderate COVID-19 infection was defined as individuals showing evidence of lower respiratory system disease either with clinical assessment or chest CT scan but not having an oxygen saturation lower than 94% on room air.

Twenty age-, sex-, and risk factor-matched healthy adults without a history of cardiac disease and COVID-19 infection were included in the control group.

The study protocol was approved by the Local Ethics Committee (decision date: November 17, 21, decision number: 2021000334-7) and was performed in concordance with the Declaration of Helsinki. All patients provided written informed consent.

Clinical, demographic characteristics, troponin I (hsTnI), and N-terminal proB-type natriuretic peptide levels on the echocardiographic exam day were recorded.

Echocardiographic Examination

All patients underwent a comprehensive echocardiographic examination with a GE E9 ultrasound machine (GE, Horten, Norway) with a 3.5-MHz transducer, following the American Society of Echocardiography guideline.[14]

Left ventricular (LV) end-systolic and end-diastolic diameters, interventricular septum, and posterior wall thickness were calculated on M-mode imaging from parasternal long-axis views. Left ventricular mass and relative wall thickness were calculated from the parasternal long-axis view, according to Devereux's formula.[15] Tricuspid annular plane systolic excursion was recorded on M-mode imaging. Left ventricular end-systolic and end-diastolic volumes and LV ejection fraction were measured using the biplane Simpson method. Early transmitral flow velocity (E), late transmitral flow velocity (A), the average of early diastolic velocities of the lateral and medial mitral annulus (e'), and tricuspid

Figure 2. Right ventricle free wall speckle tracking analysis of a patient with prior mild-moderate COVID-19 infection.

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lateral annular systolic velocity (s') were obtained by pulsed-wave Doppler and recorded from apical 4-chamber views. Accompanying valvular insufficiencies were evaluated semi-quantitatively.

Two-Dimensional Speckle Tracking Echocardiographic Analysis

The frequency was set at 60-80 Hz, and the apical 4, 3, and 2 chamber grayscale images were recorded. The recorded images were analyzed offline using a software program (EchoPAC, GE Healthcare). The LV endocardial line was tracked manually at end systole, and the software program drew an additional epicardial line; thus, a region of interest (ROI) was formed. Region of interest was corrected manually if necessary. Then the software program divided the LV into 6 segments. The peak systolic longitudinal strain value was calculated by averaging all the 18 segments (Figure 1). Right ventricular longitudinal strain (RVLS) was measured in an apical 4-chamber projection focused on the RV. The RV-free wall was divided into 3 segments. The interventricular septum was not included in the strain analysis. The strain values of the 3 segments were averaged to obtain RVLS (Figure 2).

For the calculation of left atrial (LA) longitudinal strain, the LA endocardial line was manually drawn at peak systole in the apical 4-chamber view. The software then automatically divided the LA into 6 segments, and the segments were analyzed, and an average of all segments was considered (Figure 3). For calculating right atrial (RA) longitudinal strain, RV-focused apical 4-chamber views were used. The tracing was started at the tricuspid valve annulus, followed through the endocardial border of the RA lateral wall, roof, septal wall, and ended at the opposite tricuspid annulus. The software then automatically divided the RA into 6 segments, and the segments were analyzed, and an average of all segments was considered (Figure 4). Two independent sonographers analyzed all images.

Reproducibility

Inter-observer and intra-observer variability: Images from 10 patients were randomly selected, and a second independent, blinded observer measured the images to assess the inter-observer variability. The first observer who measured all patients' views re-measured the same randomly selected 10 patients' views at least 6 weeks apart from the first measurement. Inter-observer and intra-observer variability were assessed using the intra class correlation coefficient (ICC) method. Intra-observer (ICC: 0.97, 95% CI: 0.91-0.99) and inter-observer (ICC: 0.94, 95% CI: 0.78-0.98) agreement of LA strain measurements was excellent. Intra-observer (ICC: 0.97, 95% CI: 0.91-0.99) and inter-observer (ICC: 0.94, 95% CI: 0.78-0.98) agreement of LV strain measurements were excellent. Intra-observer (ICC: 0.93, 95% CI: 0.76-0.98)
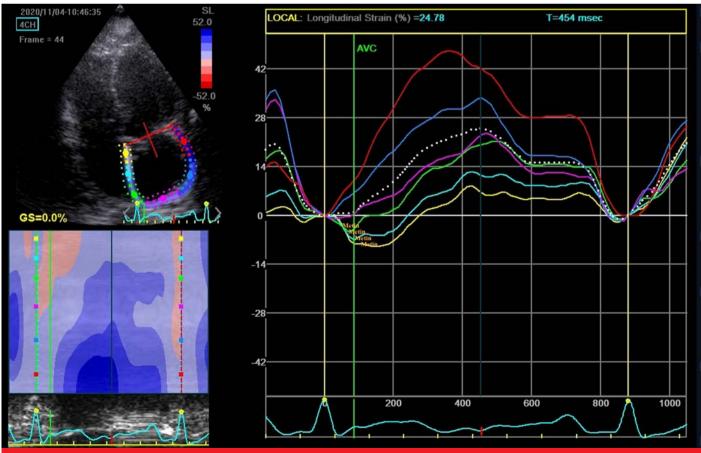

Figure 3. Left atrium speckle tracking analysis of a patient with prior mild-moderate COVID-19 infection.

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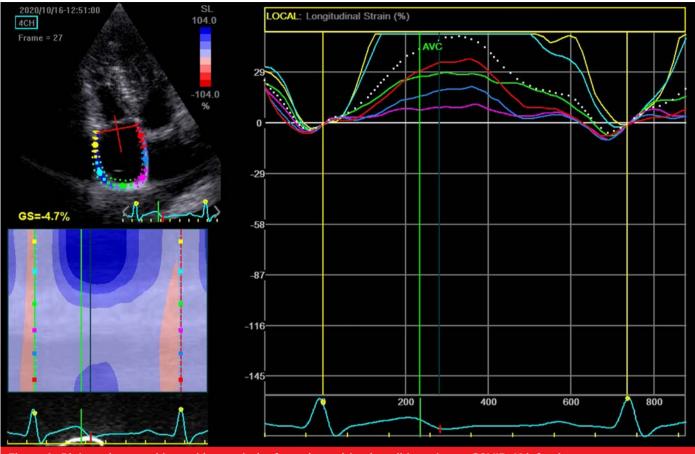Akbulut et al. Cardiac Function in COVID-19 Survivors

Figure 4. Right atrium speckle tracking analysis of a patient with prior mild-moderate COVID-19 infection.

and inter-observer (ICC: 0.91, 95% CI: 0.65-0.97) agreement of RV strain measurements was excellent. Intra-observer (ICC: 0.96, 95% CI: 0.79-0.99) and inter-observer (ICC: 0.94, 95% CI:0.80-0.98) agreement of right atrial strain measurements was excellent.

Statistical Analysis

Baseline characteristics were presented as mean ± standard deviation for continuous variables. We used the Shapiro−Wilk test to check whether the data were normally distributed across different groups. We found that most variables were not normally distributed; therefore, we used non-parametric methods for all statistical analyses. Comparison of continuous echocardiography variables was performed using the Kruskal−Wall's test for whole group analysis and the Dunn's test for the multiple pairwise comparisons used as a post-doc procedure following the Kruskal−Wallis test; the data were expressed as the median (interquartile range). Chi-square test or Fisher exact test were used for categorical variables and presented as percentages. A *P*-value <.05 was defined as statistically significant. All data were analyzed using JMP version 14.0 (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Clinical Characteristics

A total of 58 patients were included in the present study. All of the patients were tested positive for COVID-19 by RT-PCR within the previous 6 months. The clinical and demographic characteristics of the patients are shown in Table 1.

An unselected total of 20 healthy controls, of whom 12 (60%) were female, were included. The mean age was 45.6 years. One (5%) patient had diabetes mellitus and 6 (30%) patients

Table 1. Demographic and Clinical Characteristics of All Patients

Variables	Total Patients (n=58)	Control Group (n=20)
Clinical characteristics		
Age (years)	45 ± 14.63	45.6 ± 6.7
Male, n (%)	30 (51.7)	8 (40)
Smoker, n (%)	14 (24.5)	9 (45)
Pneumonia on CT, n (%)	16 (27.6)	
Hospitalization for COVID-19, n (%)	14 (31.8)	
HT, n (%)	12 (20.7)	7 (35)
DM, n (%)	5 (8.6)	1 (5)
Laboratory findings		
Troponin I levels on admission (pg/mL)	4.67 ± 1.69	4.63 ± 2.51
NT-proBNP levels on admission (pg/mL)	52.9 ± 60.2	58 ± 60

CT, computed tomography; HT, hypertension; DM, diabetes mellitus.

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Table 2. Echocardiographic Characteristics of All Patients [Data Expressed as Median (Interquartile Range)]

Echocardiographic Variables	Total Patients (n = 58)	Patients With Pneumonia on CT (n = 16)	Patients Without Pneumonia on CT (n = 42)	Control Group (n = 20)	Chi-Square/P
LVEDD (mm)	47.90 (7.0)	48.0 (4.7)	47.0(9.5)	45.0 (5.5)	3.575/0.132
LVESD (mm)	30.0 (6.2)	32.0 (7.0)	28.5 (5.5)ᵃ	30.0(9.0)ᵃ	5.597/0.061*
PW (mm)	9.0 (1.0)	10.0 (3.0)	9.0 (1.0)	9.0 (1.0)	4.456/0.108
IVS (mm)	10.0 (1.5)	8.0 (3.0)	10.0 (1.0)	10.0 (2.0)	0.966/0.617
RWT	0.38 (0.08)	0.42 (0.12)	0.38 (0.08)	0.38 (0.08)	5.458/0.065
LV mass (g)	143.0 (48.5)	153.0 (34.0)	135.0 (49.7)	148.0 (78.0)	0.900/0.638
LVEF (%)	66.0 (8.7)	64.0 (6.0)	64.5 (12.25)	70.0 (6.0)	3.722/0.156
TAPSE (mm)	21.5 (4.2)	24.0 (11.0)	22.0 (2.5)ᵇ	20.0 (4.0)ᵇ	3.786/0.151
E (m/sn)	0.7 (0.2)	0.67 (0.22)ᶜ	0.74 (0.36)ᶜ	0.62 (0.21)	6.783/0.034*
A (m/sn)	0.6(0.2)	0.59 (0.43)	0.64(0.08)	0.60 (0.22)	0.640/0.726
E/e' (mean)	6.1 (2.1)	6.0 (1.70)	5.8 (2.77)	6.6 (3.40)	1.095/0.578
S' (cm/sn)	13.0 (3.0)	14.0 (3.0)	12.5 (3.75)	13.0 (2.0)	4.196/0.123
LV global longitudinal strain (%)	−19.1 (3.9)	−20.7 (4.6)	−19.6 (2.9)	−17.1 (7.4)	1.758/0.415
RV longitudinal strain (%)	−25.9 (8.1)	−24.7 (10.5)	−26.8 (14.6)	−26.4 (9.1)	1.969/0.374
LA peak systolic strain (%)	29.9 (11.3)	28.2 (8.7)	32.6 (18.9)	30.2 (9.2)	2.138/0.343
RA peak systolic strain (%)	37.5 (18.8)	40.1(26.3)	35.1 (22.8)	39.7 (13.4)	0.511/0.774

Chi-square/P: Kruskall−Wallis test statistics and P value. *Significant on Kruskal−Wallis test; P values were for ᵃ0.020, ᵇ0.047, and ᶜ0.013 on the Mann−Whitney U test.
LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; SV, stroke volume; PW, left ventricular posterior wall; IVS, inter-ventricular septum; RWT, relative wall thickness; LV, left ventricular; LVEF, left ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion; S', tricuspid lateral annular systolic velocity; RV, right ventricular; LA, left atrial; RA, right atrial; CT, computed tomography.

had hypertension. All demographic and laboratory variables were similar between the groups.

Echocardiographic Data

The echocardiographic characteristics of the patients were summarized in Table 2.

In terms of echocardiographic variables, significant differences were observed between the groups for the variables E wave velocity, LVESD, and TAPSE (Table 2). The LVESD was significantly lower in patients with COVID-19 when compared to patients in the control group (Table 2). E wave velocity was significantly lower in patients with pneumonia on CT compared to patients without pneumonia (Table 2). Tricuspid annular plane systolic excursion was significantly higher in COVID-19 patients compared to the control group (Table 2).

Left and right ventricular longitudinal strain values and both atrial peak systolic strains did not differ between the groups.

DISCUSSION

This study demonstrates that uncomplicated COVID-19 infection had no measurable impact on both left and RV and RA functions and serum biomarkers in the long term and thus may aid in reducing unnecessary diagnostic investigations in this patient group.

Considerable myocardial damage including acute myocardial injury, acute myocarditis, arrhythmias, type 1 and 2 myocardial infarction, and acute RV failure due to ARDS or pulmonary thromboembolism occurs during COVID-19 infection.[2] Earlier studies have demonstrated that acute myocardial injury detected using troponin levels during hospitalization for COVID-19 is closely related to in-hospital mortality.[16,17] Recent studies have supported this finding by using novel imaging techniques to demonstrate both RV and LV involvement more specifically. In the ECHOVID-19 study, both LV and RV longitudinal strain and TAPSE were strongly associated with COVID-19 mortality.[6] Similarly, in a study conducted by Li et al[5] RV longitudinal strain, RV fractional area change, and TAPSE were significant predictors of mortality in COVID-19 patients.

During the COVID-19 pandemic, the excessive number of infected patients has outpaced inpatient hospital sources worldwide. As a result, most of the patients with mild-moderate disease have been followed up in an outpatient fashion. However, knowledge of cardiac involvement in this patient group is sparse. Moreover, data on long-term cardiac effects of COVID-19 in patients with mild or moderate infection are limited. For example, in a MRI study conducted by Puntmann et al[8] ongoing myocardial inflammation was observed in 60% of the patients on cardiac MRI, independent of overall disease severity and time from the diagnosis of the infection. Similarly, Brito et al[9] showed subtle pericardial enhancement in MRI studies of college student-athletes who recovered from uncomplicated COVID-19 infection, without significant abnormal findings on echocardiographic analysis. Also, in a very recent study conducted by Joy et al[10] there were no differences in cardiac structure, function, or tissue characterization on cardiac MRI images between mild COVID-19 survivors and healthy control group, 6 months after the initial infection.

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To the best of our knowledge, putting aside the study by Brito et al[9] our study is the first to investigate the long-term cardiac involvement in patients recovered from uncomplicated COVID-19 comprehensively with speckle tracking strain analysis of both ventricle and atria. Furthermore, our study is essential in providing information about the deformation parameters of both atria in adults with prior COVID-19 infection.

In this study, we did not observe a significant decline in either LV or RV systolic functions in patients with COVID-19, even those who had pneumonia, in the long term. These findings are in concordance with the results of Brito et al[9] showing no difference between healthy controls and both symptomatic and asymptomatic COVID-19 patients in terms of LV global longitudinal strain and RV free wall longitudinal strain.

Moreover, both LA and RA strain values showed no difference from the healthy controls, demonstrating no significant influence of uncomplicated COVID-19 infection on atrial functions. Our findings are contrary to Matsubara et al[18] who established a distinct decrease in LA strain in children with multisystem inflammatory syndrome following COVID-19 infection. However, LV global longitudinal strain values were also reduced in those patients which may account for the discrepancies between the results.

Troponin-I and NT-proBNP, biomarkers of myocardial injury, levels were within the normal limits in all of our patients. This finding also illustrates the absence of ongoing myocardial injury in long term in mild-moderate COVID-19 survivors. To our knowledge, there have not been any trials investigating the role of myocardial biomarkers in long-term in COVID-19 patients yet.

Study Limitations
Derivation of data from a single-center, lack of echocardiographic examination of the patients during the acute illness course, and the low sample size are the main limitations of our study.

CONCLUSION

In conclusion, long-term cardiac sequelae of COVID-19 infection continue to be an obscure clinical entity, resulting in many concerns among survivors. This results in unnecessary outpatient visits to cardiology clinics on the grounds of the ongoing pandemic, putting both patients and healthcare workers at risk. This study is valuable in setting forth the unaffected systolic and diastolic myocardial functions on long term in uncomplicated COVID-19 cases and may aid in decreasing the anxiety levels of the survivors and the number of unnecessary applications to cardiology clinics. Future studies in larger cohorts of patients are warranted to make firm conclusions.

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